REMARKS

Reconsideration of this application is respectfully requested.

In the specification, paragraphs [0003] and [0046] (paragraph numbers from the published version of the application) have been amended to correct minor editorial problems. Claims 1-34 are pending in this application. Claims 1, 9, 22, 25, and 27 have been amended and new claims 35-52 have been added to clarify the invention. Claims 9, 25, 27, 32, and 33 have been amended to correct minor editorial problems. Support for the amendments and new claims can found in the application as originally filed. No new matter has been added to this application as a result of the present amendments and new claims.

Turning now to the Office action, the specification is objected to for recitation of citation to a reference "Games, supra" without previously providing the full citation. Claims 1-34 are rejected under 35 U.S.C. §§ 101 and 112, first paragraph for allegedly not meeting the utility requirement. Claims 1-34 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly not meeting the enablement requirement. Claims 1-5, 7, 8, 17-20, 27-29, and 34 stand rejected under 35 U.S.C. § 102(e) as being unpatentable over US 2002/0157122 A1. Finally, claims 1-9, 12-21, 27-30, 32, and 34 as being unpatentable over a number of different references. The Applicants respectfully traverse these objections and rejections in the order of their appearance in the Office action.

A. Amendments to the Specification

Paragraph [0003] of the published application has been amended to correct typographical errors in the published version of the application. Support for these amendments can be found in the corresponding paragraph in the originally filed application, paragraph [07] on p. 1. Paragraph [0046] has been amended to recite the full citation for the Games reference. Support

for this amendment can be found at paragraphs [0046], [0048], and [0063] of the published application, which describe the content of the reference in detail sufficient to allow one of skill in the art to readily ascertain the full citation of the reference. Thus, no new matter has been added by the amendments to the specification.

B. Amendments to the Claims

Claims 1 and 27 have been amended to recite that the BACE-1 allele is rendered nonfunctional by deletion of exons 4-8. Support for these amendments can be found in original claim 12. Claim 9 has been amended to revise the dependency of the claim and to correct a typographical error. Support for this amendment can be found in the claims as originally filed. Claims 22 and 25 have been amended to remove the dependency from claim 1. Support for these amendments can be found in the claims as originally filed. Claims 25, 27, 32, and 33 have been amended to correct typographical errors in the claim. Support for these amendments can be found in the claim as originally filed. New claims 35-52 have been added to clarify the invention. Support for new claim 35 can be found at paragraph [0067] of the published application. Support for new claim 35 can be found at paragraph [0067] of the published application. Support for new claim 36 can be found at paragraph [0067] of the published application and original claim 8. Support for new claim 37 can be found at paragraph [0067] of the published application and original claim 12. Support for new claim 38 can be found at paragraph [0067] of the published application and in original claims 1 and 6. Support for new claims 39-52 can be found in original claims 2-4, 7, 8, 11-16, and 19-21. Accordingly, no new matter has been added to the application as a result of the present amendments.

C. **The Amendment to the Specification to Include the Full Citation for the Games Reference Does Not Constitute New Matter**

An amendment to the specification to correct an obvious error does not constitute new matter if one of skill in the art would not only recognize the existence of the error, but would also recognize the appropriate correction. *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971); M.P.E.P. § 2163.07(II). In this case, the first reference to the Games reference failed to include the full citation. One of skill in the art would recognize this error. However, the specification describes the Games reference in sufficient detail at paragraphs [0046], [0048], and [0063] that one of skill in the art can readily ascertain the proper citation. A PubMed search at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed using the search string "Games [AU] AND APP AND 717" generates two hits, only one of which lists Games as the first author. Since one of skill in the art would recognize the appropriate correction of the error, this amendment to the specification does not constitute new matter.

D. **The Claims Satisfy the Utility Requirement**

Claims 1-34 stand rejected under 35 U.S.C. 101 as allegedly lacking patentable utility and under 35 U.S.C. 112, first paragraph as allegedly lacking enablement based on the alleged lack of utility. The Office asserted that the claims "lack a specific utility because the identification of other effects that a β-secretase inhibitor would have on an animal is not directed to any particular effect." Office action at p. 3. Furthermore, the Office asserted that "using the animal to screen for proteases other than β-secretases that cause the production of a protein that is recognized by an antibody ... is not specifically directed at a specific protein." *Id.* The Office also asserted that the claims lack substantial utility. Applicants respectfully traverse the rejection.

The claims to animals and methods of using the animals have a specific utility in that the claimed animals can be used to screen for inhibitors of β-secretase activity, inhibitors of other proteases, and assay for side effects of the inhibitors. All of these uses of the animals and methods are useful in identifying therapeutics for the treatment or prevention of Alzheimer's disease. *See* paragraph [0047] of the published application. The specification clearly correlates proteolytic cleavage of APP with Alzheimer's disease. *See* paragraph [0003]. BACE-1 is one of the proteases which cleaves APP, but other proteases are involved as well. *Id.* Identification and characterization of inhibitors of these proteases is useful in identifying therapeutics for the treatment or prevention of Alzheimer's disease. Thus, the Applicants have disclosed "a specific biological activity and reasonably correlate[d] that activity to a disease condition," which is sufficient to identify a specific utility for the invention. M.P.E.P. 2107.01. Furthermore, the claims have a substantial or "real world" utility as the animals and methods of assay using the animals are relevant to the development of therapeutics for the treatment or prevention of Alzheimer's. Because the claimed invention is supported by a specific and substantial utility, the Applicants respectfully request withdrawal of the utility rejection and the companion 35 U.S.C. 112, first paragraph rejection.

E. <u>The Claims Satisfy the Enablement Requirement of 35 U.S.C. § 112, First Paragraph</u>

Claims 1-34 stand rejected under 35 U.S.C. 112, first paragraph as allegedly lacking enablement. More particularly, the Office asserted that, while the specification is enabling for methods of producing BACE-1 null mice, the methods disclosed were not enabled at the time of filing for the breadth of nonhuman animals claimed. Applicants respectfully traverse the rejection.

The standard for enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. M.P.E.P. §2164.08. The Applicants submit that one of skill in the art could make and use the claimed nonhuman animals, without undue experimentation. "The test of enablement is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 190 USPQ 214, 217-19 (CCPA 1976)); M.P.E.P. §2164.06. Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.,* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Furthermore, the fact that the experimentation needed is complex is not determinative on the issue of whether the experimentation is undue, so long as the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983).

The Office asserts that at the time of filing, the art taught that cloning was unpredictable for the breadth of the claimed nonhuman animals. However, the level of predictability in the art is but just one of the factors to consider when determining whether experimentation is undue. M.P.E.P. 2164.01(a). Also relevant to the analysis is the breadth of the claims, the nature of the invention, state of the prior art, the level of one of ordinary skill, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d at 1404; M.P.E.P. 2164.01(a).

The Examiner points out that the level of predictability for making the transgenic animal in many species may be low, but the other *Wands* factors must also be considered. "It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [Wands] factors while ignoring one or more of the other factors." M.P.E.P. 2164.01(a). In this case, the level of ordinary skill in the art is high. Furthermore, the Examiner points out that an article on cloning technology which pre-dates the present application (Westhusin) states that the basic methodology for nuclear transfer is similar across species, and then goes on to identify six factors that are relevant to successful cloning. Thus, at the time of filing, the basic methodology for cloning by nuclear transfer was known. Furthermore, the state of the art was such that it was known what factors needed particular attention for successful cloning. The application specifically points out, at paragraph [0045] (of the published application), that the nuclear transfer method is the preferred method for the generation of non-murine transgenic animals of the invention. For the murine transgenic animals of the invention, the specification provides both a general description of the methodology utilizing embryonic stem cell technology (see paragraph [0044] of the published application) and two specific examples of using embryonic stem cell technology to generated transgenic mice (see paragraphs [0067] and [0068] of the published application). Thus, the cloning tools necessary to generate the transgenic nonhuman animals of the invention were in place in the art at the time of filing. The fact that the experimentation needed to generate the claimed nonhuman animals is complex is not determinative on the issue of whether the experimentation is undue, since the art typically engages in such experimentation, and the art, at the time of filing, disclosed factors important for successful cloning.

The Applicants submit that as taught in the specification and described above, one of skill in the art could make the claimed nonhuman animals, without undue experimentation. Therefore, the claims are enabled. Applicants respectfully request withdrawal of the rejection.

F. The Claims Satisfy the Requirements of 35 U.S.C. § 102(e)

Claims 1-5, 7, 8, 17-20, 27-29, and 34 stand rejected under 35 U.S.C. 102(e) as allegedly anticipated by US 2002/0157122 A1 ('122). Applicants respectfully traverse the rejection.

A claim is anticipated only if every element of the claim is disclosed, either expressly or inherently, in a single prior art reference. M.P.E.P. § 2131. The Office asserts that the '122 reference teaches every element of the rejected claims. Claims 7 and 8 have been cancelled, thereby obviating the rejection as to these claims. Independent claims 1 and 27 have been amended to recite that the BACE-1 allele is rendered nonfunctional by deletion of exons 4-8. The '122 reference only teaches inactivation of the BACE-1 allele by deletion of exon 1 of the BACE-1 gene. Thus, the '122 reference does not teach, suggest, or inherently disclose each and every element of claims 1-5, 17-20, 27-29, and 34 as amended. Likewise, the '122 reference does not teach every element of the new claims. New claims 35-37 are directed to a method of generating a transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene using homologous recombination between the endogenous BACE-1 gene and a genetic construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. The '122 reference does not teach or suggest genetic constructs comprising frt recombination sites. New claims 38-52 are directed to transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene produced by homologous recombination between the endogenous BACE-1 gene and a construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. The

'122 reference does not teach or suggest genetic constructs comprising frt recombination sites. Thus, '122 does not anticipate any of the amended or new claims. Applicants respectfully request withdrawal of the rejection.

G. The Claims Satisfy the Requirements of 35 U.S.C. § 103(a)

Claims 1-9, 12-21, 27-30, 32, and 34 stand rejected under 35 U.S.C. 103(a) as allegedly obvious in view of a number of references. Applicants respectfully traverse the rejections in the order presented in the Office action. In view of the arguments laid out below, the Applicants respectfully request withdrawal of the rejection.

a. Mansour in view of Vassar

Claims 1-5, 7, 8, 12, 27-29, 32 and 34 stand rejected under 35 U.S.C. 103(a) as allegedly obvious based on Mansour in view of Vassar. Claims 7, 8, and 12 have been canceled, thereby obviating the rejection as to those claims. The remaining rejected claims have all been amended to require that the BACE-1 allele is rendered nonfunctional by deletion of exons 4-8. One requirement for a *prima facie* case of obviousness is that all of the claim limitations must be taught or suggested by the prior art. The Office asserts that Mansour teaches a general method for the generation of transgenic mice by homologous recombination between the target gene and a genetic construct in embryonic stem cells. However, the method disclosed by Mansour requires knowledge of the intron-exon boundaries in the target gene (page 348, third paragraph of text: "A cloned fragment of the gene must be available and the intron-exon boundaries with that fragment defined."). As noted by the Examiner, Mansour does not teach the genomic sequence of the target gene, in this case, BACE-1. This deficiency in Mansour is not overcome by the teaching in Vassar. While Vassar teaches a genetic sequence identified as BACE, the sequence disclosed is a cDNA sequence, thus, it would not be expected to be the full-length

BACE gene containing both introns and exons. Vassar does not teach or suggest any of the intron-exon boundaries in the disclosed sequence. Thus, the references, even when combined, do not teach all of the limitations of the rejected claims.

The teaching of Mansour in view of Vassar likewise does not render any of the new claims obvious. New claims 35-37 are directed to a method of generating a transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene using homologous recombination between the endogenous BACE-1 gene and a genetic construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. Mansour does not teach or suggest using frt recombination sites. This deficiency in Mansour is not overcome by the teaching of Vassar as Vassar merely teaches the cDNA sequence of BACE. New claims 38-52 are directed to transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene produced by homologous recombination between the endogenous BACE-1 gene and a construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. Mansour does not teach or suggest using frt recombination sites. This deficiency in Mansour is not overcome by the teaching of Vassar as Vassar merely teaches the cDNA sequence of BACE. Thus, the references, even when combined, do not teach all of the limitations of the new claims.

b. <u>Mansour in view of Vassar and Wattler</u>

Claims 1, 6, 8, 9, 27, and 30 stand rejected under 35 U.S.C. 103(a) as allegedly obvious based on Mansour in view of Vassar and Wattler. Claim 8 has been canceled, thereby obviating the rejection as to that claim. The remaining rejected claims have all been amended to require that the BACE-1 allele is rendered nonfunctional by deletion of exons 4-8. As discussed above, the method disclosed by Mansour requires knowledge of the intron-exon boundaries in the target

gene (page 348, third paragraph of text: "A cloned fragment of the gene must be available and the intron-exon boundaries with that fragment defined."). As noted by the Examiner, Mansour does not teach the genomic sequence of the target gene, in this case, BACE-1. This deficiency in Mansour is not overcome by the teaching in Vassar as Vassar does not teach or suggest any of the intron-exon boundaries in the disclosed sequence. Nor is this deficiency overcome by the teaching of Wattler, as this reference teaches a general method of mutagenesis through gene disruption. Thus, the references, even when combined, do not teach all of the limitations of the rejected claims.

The teaching of Mansour in view of Vassar and Wattler likewise does not render any of the new claims obvious. New claims 35-37 are directed to a method of generating a transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene using homologous recombination between the endogenous BACE-1 gene and a genetic construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. New claims 38-52 are directed to transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene produced by homologous recombination between the endogenous BACE-1 gene and a construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. The method disclosed by Mansour requires knowledge of the intron-exon boundaries in the target gene. This deficiency in Mansour is not overcome by the teaching of Vassar as Vassar merely teaches the cDNA sequence of BACE without providing any teaching of the intron-exon boundaries. The deficiencies of Mansour and Vassar are not overcome by the teaching of Wattler as this reference teaches a general method of mutagenesis through gene disruption. Thus, the references, even when combined, do not teach all of the limitations of the new claims.

c. **Farhangrazi in view of Mansour and Vassar**

Claims 19 and 20 stand rejected under 35 U.S.C. 103(a) as allegedly obvious based on Farhangrazi in view of Mansour and Vassar. The rejected claims have all been amended to require that the BACE-1 allele is rendered nonfunctional by deletion of exons 4-8. As discussed above, the method disclosed by Mansour requires knowledge of the intron-exon boundaries in the target gene (page 348, third paragraph of text: "A cloned fragment of the gene must be available and the intron-exon boundaries with that fragment defined."). As noted by the Examiner, Mansour does not teach the genomic sequence of the target gene, in this case, BACE-1. This deficiency in Mansour is not overcome by the teaching in Vassar as Vassar does not teach or suggest any of the intron-exon boundaries in the disclosed sequence. Nor are these deficiencies overcome by the teaching of Farhangrazi, as this reference merely teaches the use of cortical cells as tools in research related to Alzheimer's disease. Thus, the references, even when combined, do not teach all of the limitations of the rejected claims.

The teaching of Mansour in view of Vassar and Farhangrazi likewise does not render any of the new claims obvious. New claims 35-37 are directed to a method of generating a transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene using homologous recombination between the endogenous BACE-1 gene and a genetic construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. New claims 38-52 are directed to transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene produced by homologous recombination between the endogenous BACE-1 gene and a construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. The method disclosed by Mansour requires knowledge of the intron-exon boundaries in the target gene. This deficiency in Mansour is not

overcome by the teaching of Vassar as Vassar merely teaches the cDNA sequence of BACE without providing any teaching of the intron-exon boundaries. The deficiencies of Mansour and Vassar are not overcome by the teaching of Farhangrazi as this reference generally teaches the use of cortical cells in Alzheimer's related research. Thus, the references, even when combined, do not teach all of the limitations of the new claims.

d. US 2002/0157122 A1 in view of Games

Claims 1, 13-19, and 21 stand rejected under 35 U.S.C. 103(a) as allegedly obvious based on US 2002/0157122 A1 in view of Games. Claim 1 has been amended to recite that the BACE-1 allele is rendered nonfunctional by deletion of exons 4-8. The remaining rejected claims depend from claim 1. The '122 reference only teaches inactivation of the BACE-1 allele by deletion of exon 1 of the BACE-1 gene. Thus, the '122 reference does not teach, suggest, or inherently disclose each and every element of claims 1, 13-19, and 21. This deficiency is not overcome by the teaching of Games. Games teaches transgenic mice expressing mutated APP. Games does not teach BACE-1 knockout mice. Thus, the references, even when combined, do not teach all of the limitations of the rejected claims, as amended.

Likewise, the '122 reference in view of Games does not teach every element of the new claims. New claims 35-37 are directed to a method of generating a transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene using homologous recombination between the endogenous BACE-1 gene and a genetic construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. Neither the '122 reference nor Games teaches or suggests genetic constructs comprising frt recombination sites. New claims 38-52 are directed to transgenic nonhuman animal comprising at least one nonfunctional allele of the BACE-1 gene produced by homologous recombination

between the endogenous BACE-1 gene and a construct comprising a positive selection marker, a portion of the BACE-1 sequence and frt recombination sites. Neither the '122 reference nor Games teaches or suggests genetic constructs comprising frt recombination sites. Thus, the references, even when combined, do not teach all of the limitations of the new claims.

CONCLUSION

In view of the amendments and remarks above, the application is considered to be in proper form for allowance. Therefore, the Patent Office is respectfully requested to pass the application to issue. If the Office is of the opinion that a teleconference would expedite the prosecution of the application, the Examiner is encouraged to contact Applicants' undersigned representative.

Respectfully submitted,

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